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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HEYER, DENNIS

ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
06/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/824,695	ONER ET AL.	
	Examiner	Art Unit	
	DENNIS HEYER	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/8/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/8/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 8, 2010 has been entered.

Acknowledgement is made of Applicant's remarks filed February 8, 2010. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of Claims

Claims 1 – 11 are currently pending

Information Disclosure Statement

The information disclosure statement (IDS) submitted on February 8, 2010 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim rejections – 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 – 11 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in Ex parte Wu, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of Ex parte Steigewald, 131 USPQ 74 (Bd. App. 1961); Ex parte Hall, 83 USPQ 38 (Bd. App. 1948); and Ex parte Hasche, 86 USPQ 481 (Bd. App. 1949). In the present

instance, Claims 1, 10 and 11 recite the broad recitation “at the most 10% w/v of alendronate dissolved”, and the claim also recites “no dissolved alendronate”, which is the narrower statement of the range/limitation.

Claim 1 is drawn to a product (a pharmaceutical formulation) and a process (oral administration after dispersing in water). A single claim that claims both a product and a method of using the product is ambiguous (MPEP 2173.05(p) (II)). For the purpose of examination on the merits any prior art reading on the product will be considered to meet the limitation of the claimed process: administered orally after dispersing in water.

Claim rejections - 35 USC § 101

The following is a quotation of the first paragraph of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 - 11 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is directed to neither a “product’ nor a “process" but rather embraces or overlaps two different statutory classes set forth in 35 U.S.C. 101 which is drafted so as to set forth the statutory classes in the alternative only (MPEP 2173.05(p) (II)). In the instant case the Claims embrace or overlap a product (a pharmaceutical formulation) and a process for using the product (oral administration after dispersing in water). It is noted that claims 1 – 11 are also rejected under 35 U.S.C. 112 2nd paragraph as being indefinite.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uslu, A. in WO 03/043641 (filed: October 15, 2002) in view of Watanabe *et al.* in US 2002/0150624 (published: October 17, 2002), Bogataj *et al.* in Drug Development and Industrial Pharmacy 15 (14 – 16), 2295 – 2313 (1989), De Groen *et al.* in The New England Journal of Medicine 1996;335:1016 – 21, Palepu, P.R. US 2003/0064966 (published: April 3, 2003), Black *et al.* in US 2001/0051636 (published: December 13, 2001) and Tritthart *et al.* in US patent 6,242,002 (published: June 5, 2001).

The Uslu, Watanabe, Tritthart and Black references were previously applied in the Office Action mailed 9/11/2009.

Uslu teaches a pharmaceutical formulation administered orally containing alendronate mixed with alginic acid or sodium alginate as a powder or in granule form (page 6, lines 1 – 8). The alginic acid or sodium alginate are used in amounts ranging from 1 mg to 2000 mg (page 5, lines 1 – 4, Claim 4) sufficient to prevent esophageal reflux ('a therapeutically effective amount'; page 2, lines 22 – 27, Claim 1). Uslu does not teach a coating for the alginates, accordingly, absent specific evidence to the contrary, one of ordinary skill would reasonable construe the alginates of Uslu to be uncoated (instant Claims 1, 10 and 11). Uslu teaches dosage forms comprising the bisphosphonate alendronate sodium (Fosamax®) (alendronate monosodium trihydrate, page 2, lines 18 – 20, page 3, lines 8 – 15) is used to prevent loss of calcium in bones with amounts ranging from 1 – 1000 mg (page 3, lines 8 – 15, Claim 5; instant Claim 8). The ranges taught by Uslu for alginates (1 – 2000 mg) and alendronate (1 – 1000 mg) reads on the % weight/volume of alendronate (0.001% to 3%) and alginates (0.001% to 2%) when dissolved in 250 mL of water as recited in instant Claims 7 and 9.

Uslu teaches formulations comprising lubricants, glidants, fillers and excipients such as aerosil (colloidal silica) and microcrystalline cellulose (page 5, lines 2 – 6 and 23 – 24; instant claims 2, 3, 10 and 11).

Uslu teaches that the active alendronate composition is prepared by a wet granulation procedure (an aggregation) in which, preferably polyvinylpyrrolidone (PVP) is used (page 5, lines 14 – 21; instant Claim 11).

Uslu teaches the weights of alendronate and alginate in the formulation of instant Claim 1 but does not teach dispersing the formulation in a glass of 250 mL of water nor does Uslu teach the alendronate dissolution profiles recited in instant Claim 1 (b) and (c). Uslu also does not teach alendronate coated with a polymer soluble in gastric pH of 1 to 4 and insoluble in salivary pH of 6 to 7.5 or a formulation comprising sweeteners, or sachet dosing. Uslu teaches alendronate particles as granules but does not expressly teach 'microparticles'.

Palepu teaches treatment of bone disease in humans by administration of a bisphosphonate in an inhalation form (Abstract). Palepu teaches dissolution of coated and uncoated alendronate beads in 0.1 N HCl and pH 6.8 buffer (Fig. 3 and 4). Palepu teaches particle sizes of alendronate no greater than 100 microns (microparticles) in diameter (p [0015]). Palepu teaches drug release of coated and uncoated alendronate beads at 0.1 N HCl and pH 6.8 buffer (Fig. 3 and 4). Palepu teaches greater than 80% of the uncoated alendronate particles are released within 10 minutes in 0.1 N HCl (Fig. 3).

Uslu in combination with Palepu does not teach dispersing the formulation in a glass of 250 mL of water nor do the references teach alendronate coated with a polymer soluble in gastric pH of 1 to 4 and insoluble in salivary pH of 6 to 7.5. Uslu in combination with Palepu also does not teach a formulation comprising sweeteners, or sachet dosing.

De Groen teaches esophagitis associated with the use of alendronate (Title). De Groen teaches that alendronate is dosed at 40 mg/day to treat woman with

postmenopausal osteoporosis (page 1016, right column, 1st paragraph). De Groen teaches swallowing alendronate with 180 to 240 mL water to reduce the potential for esophegeal irritation (page 1016, Conclusions).

Uslu in combination with Palepu and De Groen does not teach alendronate coated with a polymer soluble in gastric pH of 1 to 4 and insoluble in salivary pH of 6 to 7.5 or a formulation comprising sweeteners, or sachet dosing.

Watanabe teaches pharmaceutical compositions for oral use that use the polymer Eudragit E 100 (i.e. poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) in a 1:2:1 ratio) as a coating to improving taste masking, moisture resistance and particularly in the case of bisphosphonates, such as alendronate, improving solubility and adsorption (p [0005], [0016], [0017] and [0028] and Example 1; instant claims 1, 5, 6 and 10).

Watanabe teaches Eudragit is a film coating used for taste masking, moisture resistance and particularly in the case of bisphosphonates, such as alendronate, improving solubility and adsorption. Watanabe does not explicitly teach that Eudragit E is soluble at gastric pH juices and insoluble at salivary pH.

Bogataj teaches bacampicillin microspheres coated with Eudragit E (Title, Abstract). Bogataj teaches that Eudragit E is soluble in solution to pH 5 whereas above pH 5 it becomes insoluble. Bogataj teaches Eudragit E film coatings are resistant to saliva which means that any unpleasant tastes are reliably masked on administration (page 2297, 2nd paragraph).

The combination of Uslu, Palepu, De Groen, Watanabe and Bogataj do not teach alendronate formulated in sachets with sweetening agents.

Black teaches the use of bisphosphonates, such as alendronate in sachets with sweetening agents (p [0032], [0110] and [0111]; instant Claim 2).

Black does not teach the specific sweetening agents recited in Claim 4.

Tritthart teaches sweeteners such as saccharin and sucrose are commonly used in sachets to improve flavor and taste (Claims 2 and 16: instant Claims 1, 4, 10 and 11. Tritthart also teaches that sachets are useful forms for adapting formulation to be dissolved in water before being taken (Claim 2).

Instant Claim 11 contains limitations drawn to the process by which the composition is prepared. For example: “microparticles aggregated with polyvinylpyrrolidone dissolved in ethanol and coated with a polymer…” and “said polymer in admixture with ethanol, acetone". The patentability of product-by- process limitations within a claim is based on the product itself. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698,227 USPQ 964,966 (Fed. Cir. 1985). In the instant Case the burden is shifted to Applicant to prove that the instantly Claimed formulation prepared by the recited process is us distinct from that rendered obvious by the cited combination of references.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the alendronate-alginate granule composition of Uslu by coating alendronate with Eudragit E 100, adding sweeteners and formulating as a sachet. One would have been motivated to do so because Watanabe teaches that coating alendronate with Eudragit E 100, a polymer that is soluble in solution to pH 5 and resistant to the pH of saliva (Bogataj) improves taste, moisture resistance, solubility and adsorption. One would have been motivated to add sweeteners and formulate in a sachet because Black in combination with Tritthart teaches sweeteners such as saccharin and sucrose are commonly used to improve flavor and taste and that sachets are useful forms for dispersing formulations in water before administration.

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to disperse the coated alendronate/alginate composition in 250 mL water and thus arrive at the claimed weight/volume percents. One would have been motivated to do so because De Groen teaches that swallowing alendronate with 180 to 240 mL water reduces the potential for esophegeal irritation. Absent any specific evidence to the contrary, one of ordinary skill would reasonably select water at 25 ^{o}C and pH 6 – 7.5 as this represents 'room temperature' and the pH is in the neutral range (salivary pH) typically found for water and thus the Eudragit E coating would not prematurely dissolve.

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to formulate the Eudragit E-coated alendronate granules rendered obvious by Uslu in combination with Watanabe and Bogataj as microparticles.

One would have been motivated to do so because Palepu teaches that uncoated alendronate microparticles rapidly dissolve (>80% within 10 minutes in gastric pH). Accordingly, one of ordinary skill would have recognized that microparticles of alendronate rapidly dissolve following dissolution of the Eudragit E coating in the stomach (gastric pH) and thus are readily available for absorption into the systemic circulation.

Response to Arguments

Applicant's arguments filed February 10, 2010 with respect to the rejection under 35 U.S.C 103(a) of Claims 1 – 11 as being unpatentable over Uslu (WO 03/043641) in view of Watanabe *et al.* (US 2002/0150624), Black *et al.* (US 2001/0051636) and evidenced by Tritthart *et al.* (US 6,242,002) have been fully considered but are not found to be persuasive.

Applicant contends that the instantly claimed granular composition of Uslu is distinguished from that taught by the prior art references because the references do not teach the limitation that alendronate is a microparticle (Remarks, page 2 – 4). Applicant cites "Microencapsulation Technology" to argue that the microencapsulation technique produces small particles ranging from 1 to 1000 µm (Remarks, page 4, 2nd paragraph).

This argument is not found to be persuasive because, as noted in the Final Office Action mailed September 11, 2009, Applicant discloses and claims compositions comprising alendronate microparticles but fails to offer a special definition of microparticles or any particle size range (typically such a limitation is recited in microns

or mesh size). Accordingly, any range reasonably construed to be within the range of a microparticle (such as 1 – 1000 microns) is considered to read on the claimed microparticles. As noted in the instant Office Action, the teaching of microparticles of alendronate and their dissolution properties by the Palepu reference renders obvious modifying the size of the granules of Uslu as microparticles.

Conclusion

Claims 1 – 11 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DENNIS HEYER whose telephone number is (571)270-7677. The examiner can normally be reached on Monday-Thursday 8AM-5PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, PADMANABHAN SREENIVASAN can be reached at (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DH

/Timothy P Thomas/
Examiner, Art Unit 1628